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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,698	12/11/2003	Karl Tryggvason	94,778-H-CO	4581

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EXAMINER	
PHAM, AUDREY S	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,698	TRYGGVASON ET AL.	
	Examiner	Art Unit	
	Audrey S. Pham	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 34-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 34-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: 4 published references cited in Action.

DETAILED ACTION

Re: Tryggvason *et al.*

Date of Priority: 10/04/1994

Claims 34-42 are pending.

Objections - Specification

The specification is objected to because of numerous misspelled or undefined terms. Appropriate correction is required. Some examples are provided in the following:

1. memebrane - page 1, line 26
2. contiains – page 2, line 15
3. nucelic – page 3, line 31
4. availible – page 3, lines 32 and 35
5. specfically – page 5, line 32
6. abberant – page 6, line 3
7. interverntion – page 6, line 4

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention. According to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998), the claimed invention should be enabled so that any person skilled in the art can make and use the invention without undue experimentation. See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). See also MPEP § 2164.01(a) and § 2164.04.

Factors to consider in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). The factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn broadly to methods for inhibiting tumor cell invasion, tumor cell budding, or interaction with basement membranes, comprising administering to an individual in need thereof an antibody to a laminin 5 gamma 2 chain to inhibit tumor cell invasion on non-malignant tissue in the individual. Thus, the claims broadly encompass methods of inhibiting or treating human cancer patients comprising administering antibodies.

However, the claimed invention is not enabled because there is insufficient guidance and objective evidence to predictably enable one of ordinary in the art to use the invention as claimed.

For example, the specification teaches (page 5) that the identification of the role of the gamma 2 chain allows for novel "therapeutic intervention" of binding between laminin 5 and its ligand, thereby reducing the tumor cell/basement membrane adhesion that is crucial for the invasion of non-malignant tissue. More specifically, the specification proposes (page 6) that this intervention can be achieved with monoclonal and or polyclonal antibodies anti-gamma2 chain antibodies.

However, the specification does not teach *any* antibodies that actually bind to and or inhibit the activity of a laminin 5 gamma 2 chain. Further, the specification fails to show any correlation between the biological intervention of laminin 5 gamma 2 and the inhibition of tumor cell invasion, or budding of tumor cells. In effect, the claims broadly encompass the inhibition of metastasis and the specification only proposes that such inhibition would lead to the inhibition of tumor cell invasion.

Those of ordinary skill in the art recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American, July 1994) discloses barriers to the delivery of drugs into solid tumors. These implications include: (1) non-uniform delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas receive no therapeutic agent at all (pg 60, col. 3); (2) increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) high liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (pg 61, col 1 paragraph 1); and (4) convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature (convention is not observed in tumors larger than ½ centimeter in diameter, pg 62, col 1). Further, in the late 80's, Dillman (Annals of Internal Medicine, Vol 111, pgs 592-603, 1989) summarized the status of *in vivo* use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology. Many major hurdles persist (see abstract) including

tumor cells heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). More recently, Weiner (Seminars Oncology, Vol. 26, No. 4, pgs 41-50, 1999) provided an overview of monoclonal antibody of therapy including some promising activity. However, major obstacles to clinical efficacy still exist underscoring the unpredictability of this treatment. These obstacles include impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Thus, one of ordinary skill in the field on oncology would not expect that the claimed invention would be effective for treating tumor cells invasion.

Furthermore, the disclosure of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. The specification provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success. The art teaches that the treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, pp 1041-1042, 1997), who discusses the shortcomings of potential anti-cancer agents including extrapolating from *in vitro* to *in vivo* protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drug have shown activity in either cell or animal models, but only 39 are used exclusively for chemotherapy, as opposed to supportive care, and have won approval from the FDA (pg 1041, 1st col). Wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive, the obstacle of unpredictability of cancer therapy underscore the criticality of workable examples -- which is not disclosed in the specification.

In view of the teachings above, and the lack of guidance and/or examples in the specification, it would not be predictable for one of ordinary skill in the art to use the antibody to inhibit tumor invasion. With the claims broadly drawn, the guidance limited, and the art being unpredictable, it would require

undue experimentation for one of ordinary skill in the art to successfully practice the invention as claimed.

Conclusion

No Claim is allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Audrey S. Pham whose telephone number is (571) 272-3323. The examiner can normally be reached on 8:00 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached at (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned: (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Audrey S. Pham
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Art Unit 1642

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER